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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,557	05/24/2001	Scott Hammond	CSHL-P02-010	4804

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,557	BEACH ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-15,28 and 43-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9-15, 28, 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed February 8, 2005 is acknowledged and has been entered. Claim 1 and 48 has been amended. Claims 2-8, 11, 16-27 and 29-42 have been canceled. Claims 1, 9-15, 28, 43-48 are pending. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Petition under 37 C.F.R. 1.48(b)

3. In view of the papers filed December 17, 2004, the inventorship in this nonprovisional application has been changed by the deletion of David Beach, Emily Bernstein and Amy Caudy.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Declaration

4. The declaration filed on 11/14/2004 under 37 CFR 1.131 is sufficient to overcome the previous rejections under 35 USC 102(e) as being anticipated by Li et al. The declaration establishes reduction to practice prior to Li et al. It is noted that the declaration has no effect

over the instant invention based on Applicant's amendment, which changes the scope of the invention.

New Ground(s) of Rejections

THE NEW GROUNDS OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

New Matter Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 9-15, 28, 43-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is drawn to "a method for attenuating expression of a target gene in mammalian cells, comprising introducing into mammalian cells suspended in culture an expression vector encoding a hairpin RNA which when transcribed from said expression vector in said mammalian cells attenuates expression of the target gene, wherein the transcribed hairpin RNA; (i) is a single nucleic acid strand having a double stranded portion

including first nucleotide sequence that hybridizes under stringent wash conditions of 02. x SSC at 65 degrees Celsius to a portion of the target gene, and a second nucleotide sequence which is complementary inverted repeat of said first nucleotide sequence and hybridizes to said first nucleotide sequence to form a hairpin structure; (ii) is a substrate for cleavage by an RNaseIII enzyme to produce a double stranded RNA product, (iii) does not produce a general sequence-independent killing of the mammalian cells, and (iv) reduces expression of said target gene in a manner dependent on the sequence of said double stranded portion of the hairpin RNA. The dependent claims 9-15, 28, 43-47 all relate back to the limitations of claims 1. The independent claim 48 recites the limitations presented in claim 1. Applicant cites page 26, lines 2-8 and pages 43-44 and Example 3. No-where in the cited support is there a teaching of a method for attenuating expression of a target gene in mammalian cells comprising introducing into mammalian cells suspended in culture an expression vector encoding a hairpin RNA wherein said transcribed hairpin RNA has the properties described in claims 1 and 48 and dependent claims 9-15, 28, 43-47. The cited support at page 26, lines 2-8 broadly describes methods known in the art for introducing nucleic acids to cells. The cited support at pages 43 and 44 of Example 3, discloses the introduction of double-stranded RNA by injection, transfection or feeding into C. elegans, Drosphila, plants and numerous other systems. The cited support at pages 43-44 further states the following:

> "[R]ecently, stable interference with gene expression has been achieved by expression of RNAs that forms snap-back or hairpin structures (refs 2-7). This has the potential not only to allow stable silencing of gene expression but also inducible silencing as has been observed in trypoansomes and adult Drosophila (refs 2, 4,5). The utility of this approach is somewhat hampered by the difficulties that arise in the construction of bacterial plasmids containing the long inverted repeats that are necessary to provoke silencing. In a recent report, it was stated that more than 1,000 putative clones were screened to identify the desired construct (ref 7). The presence of hairpin structures often induces

> plasmid rearrangement, in part due to the Ecoli sbc protein that recognizes and cleaves cruciform DNA structures (ref 8). We have developed a method for the construction of hairpins that does not require cloning of inverted repeats, per se. Instead, the fragment of the gene that is to be silenced is cloned as a direct repeat, and the inversion is accomplished by treatment with a site-specific recombinase, either in vitro (or potentially *in vivo* (see Fig 27). Following recombination, the inverted repeat structure is stable in a bacterial strain that lacks an intact SBC system (DL759). We have successfully used this strategy to construct numerous hairpin expression constructs that have been successfully used to provoke gene silencing in Drosophila cells."

Nowhere in the specification is the limitations recited in the claims. The cited support or specification do not teach or suggest, "Introducing into mammalian cells a expression vector encoding a hairpin RNA". In fact, the specification only suggests an association of hairpin structures with Drosophila cells, bacterial cells and possibly plants, not mammalian cells. Likewise the cited support at page 43 and 44, which discusses hairpin structures, relies on disclosure in the art as noted by the literature citations at pages 44 and 45. MPEP 608.01(p) speaks to the issue of the completeness of the specification for the practice of a claimed invention, stating, "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

Still further, there is no teaching or disclosure which describes a "transcribed hairpin RNA" or a "hairpin structure" having the characteristics recited in the claims at (i) through (iv) of claim 1 and 48. No disclosure is provided which teaches the hairpin structure being associated with primate cells or human cells as recited in the dependent claims. No disclosure is provided in the specification that provides any length limitations for the hairpin structure as required by the dependent claims. No disclosure is provided in the specification that suggests

that the hairpin structure does not cause activation of a protein kinase activated sequence-independent response in the mammalian cells. Based on the lack of support for the claimed invention, the specification would not have suggested to the skilled artisan that the applicant was in possession of the claimed invention as of the filing date of the application.

Claim Rejections - 35 USC § 112: Lack of enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 9-15, 28, 43-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*. ~~The claimed invention is drawn to~~

The claimed invention is drawn to "a method for attenuating expression of a target gene in mammalian cells, comprising introducing into mammalian cells suspended in culture an expression vector encoding a hairpin RNA which when transcribed from said expression vector in said mammalian cells attenuates expression of the target gene, wherein the transcribed hairpin RNA; (i) is a single nucleic acid strand having a double stranded portion including first nucleotide sequence that hybridizes under stringent wash conditions of 02. x SSC at 65 degrees Celsius to a portion of the target gene, and a second nucleotide sequence which is complementary inverted repeat of said first nucleotide sequence and hybridizes to said first nucleotide sequence to form a hairpin structure; (ii) is a substrate for cleavage by an RNaseIII enzyme to produce a double stranded RNA product, (iii) does not produce a general sequence-independent killing of the mammalian cells, and (iv) reduces expression of said target gene in a manner dependent on the sequence of said double stranded portion of the hairpin RNA. The specification as filed only provides sufficient guidance and/or instruction for using double stranded RNA within cells, specifically Drosophila cells, in an *in vitro* environment, but provides no support anywhere for using "hairpin RNA" or "transcribed hairpin RNA" as described in the claims in an *in vitro* environment or in an *in vivo* environment, which also encompasses cells in a whole organism. The specification as filed does not provide sufficient guidance such that an ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the hairpin RNA of the instant claims in methods of attenuating expression of a target gene or in a method of gene therapy. The specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use the hairpin RNA that would results in the desired effect. In fact, the

specification appears to rely on teachings in the art as noted by the literature citations as pages 43-45. MPEP 608.01(p) speaks to the issue of the completeness of the specification for the practice of a claimed invention, stating, "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." The only correlation the specification provides for the use of a hairpin construct is in the teaching at page 44, lines 12-14, which states that "We have successfully used this strategy to construct numerous hairpin expression constructs that have been successfully used to provide gene silencing in Drosophilia cells" (*not mammalian cells as claimed).* Even assuming that an effective construct is constructed, it is not evident that enough mammalian cells can be transfected to provide any therapeutic benefits. In fact, the specification at page 43-44 states that the "utility of this approach is somewhat hampered by the difficulties that arise in the construction of bacterial plasmids containing the long inverted repeats that are necessary to provoke silencing." Even moreso, Ech and Wilson (Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, pages 77-101, 1996) teach that there are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, et), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount of stability of the protein produced, and the protein's compartmentalization

within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the diseased being treated or desired outcome. Additionally, Marshall (Science, Vol. 269, pages 1050-1055, August 1995) states "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, col. 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, col. 2).

In the instant case, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired RNA molecule is produced in a therapeutic amount to correct or attenuate a defect in a diseased cells. Neither the specification as filed, nor the state of the prior art at the time the invention was made provides any specific guidelines in this regard. The deficiencies in specification would constitute undue experimentation since these steps must be achieved without instruction from the specification before one is enable to practice the claimed invention commensurate fully in scope.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the lack of information concerning the hairpin RNA construct and its use in attenuating gene expression, the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo,* and

the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require, producing a hairpin RNA construct and determining modes of delivery in mammalian cells including a whole organism such that the expression of a single gene is replaced or attenuated and the desired secondary effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiency in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enable to practice the claimed invention fully commensurate in scope. Therefore, in view of the foregoing, undue experimentation is required to make and use the claimed invention.

Conclusion

9. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

Kenneth R. Horlick
4/11/05